Cytoskeleton

Introduction

The **components** of the cytoskeleton are **microtubules**, **microfilaments** (actin), and **intermediate** filaments. This section focuses on microtubules and their roles. We'll discuss actin and intermediate filaments in the epithelium lesson of this series (#9: *Epithelium*), and we'll discuss the specific role of microtubules in mitosis in the Inflammation and Neoplasia series.

Microtubules

Microtubules are the **largest** of the cytoskeleton elements, and are rapidly deployed, assembled, and disassembled inside a cell. They are the scaffolding on which other proteins and vesicles move, and they act as the mechanism through which cell division separates chromosomes.

Microtubules are made of **dimers** of α-tubulin and β-tubulin. Because the α and β are different, they are referred to as **heterodimers**. In the assembly of a microtubule, the tubulin heterodimers aggregate one at a time to the growing end of the microtubule. They are added in a spiral pattern, creating a cylinder with a hollow core. The disassembly of a microtubule is very different. The entire microtubule unzips, falling apart not as the discrete heterodimers that occasioned the assembly, but rather as strings of tubulin heterodimers called **protofilaments**. This is important to realize—microtubules are **assembled** one tubulin heterodimer at a time at the growing end, but **disassemble** as continuous strings of tubulin heterodimers called protofilaments (Figure 4.1).

The microtubule's diameter (outer tubulin to outer tubulin, across the hollow core) is **25 nm**; the **hollow core's** diameter is **10 nm.**

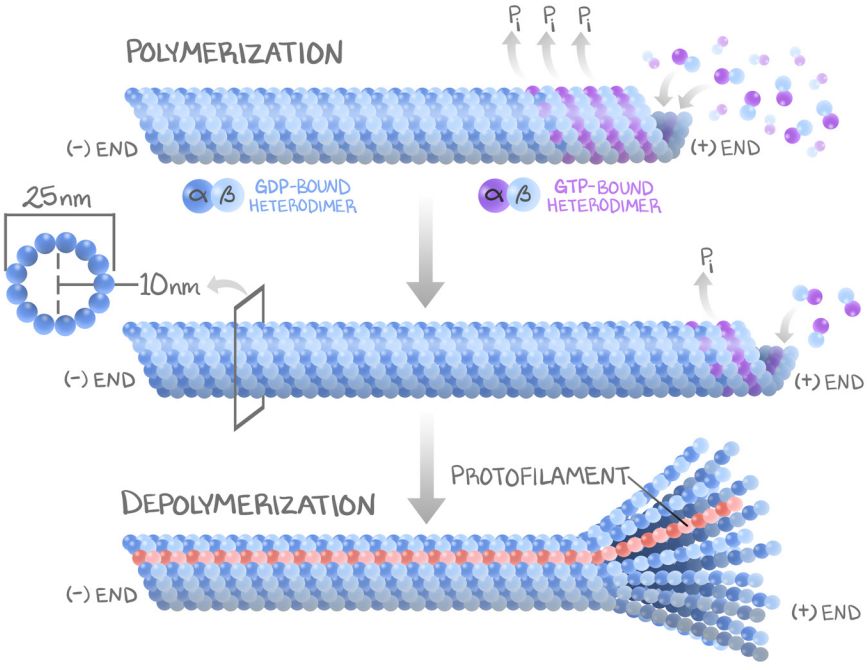


Figure 4.1: Microtubules
Microtubules are made of α-tubulin:β-tubulin heterodimers. GTP-bound heterodimers add to the growing end in a spiral formation. The diameter is 25 nm, with a hollow core of 10 nm in diameter. If the GTP cap continues in a high-energy state, more dimers will be added. Over time, GTP hydrolyzes to GDP. The heterodimers in the microtubule are stable. But if the GTP cap becomes hydrolyzed to GDP, the entire microtubule disassembles, unzipping as long strings of tubulin heterodimers called protofilaments.

Microtubules are polarized—they have a minus end and a plus end. These ends are not charged; they are just labels. In general, microtubules **anchor** at their **minus end** and **grow** at their **plus end**. Microtubule-Associated Proteins (**MAPs**), such as **τ (tau)**, maintain the microtubules in a stable, **GTP-bound** state. As long as the plus end of a microtubule is GTP-bound, the microtubule can accept more dimers to that end. Should those MAP proteins fail to protect that **GTP cap**, the natural hydrolysis activity of the tubulin dimers results in cleavage of phosphate from GTP, leaving the dimers GDP-bound. **GDP-bound dimers disassociate** from each other, and the entire tubule falls apart, unzipping as long strings—protofilaments. The microtubule is either stable and growing one heterodimer at a time, or the entire microtubule falls apart as protofilaments.

Microtubules in Transport of Vesicles

All cells use microtubules and associated motor proteins to shuttle vesicles within the cell. Neuronal axons are often-used examples of this relationship, as we have thoroughly characterized two motor proteins: kinesin and dynein. **Kinesin** moves anterograde (**towards the plus end**), from the nucleus to the periphery. **Dynein** moves retrograde (**towards the minus end**), from periphery to the nucleus. Microtubules act as tracks along which these proteins carry their cargo, the vesicle, using ATP for energy. Dynein also has additional functions, discussed in the section on cilia.

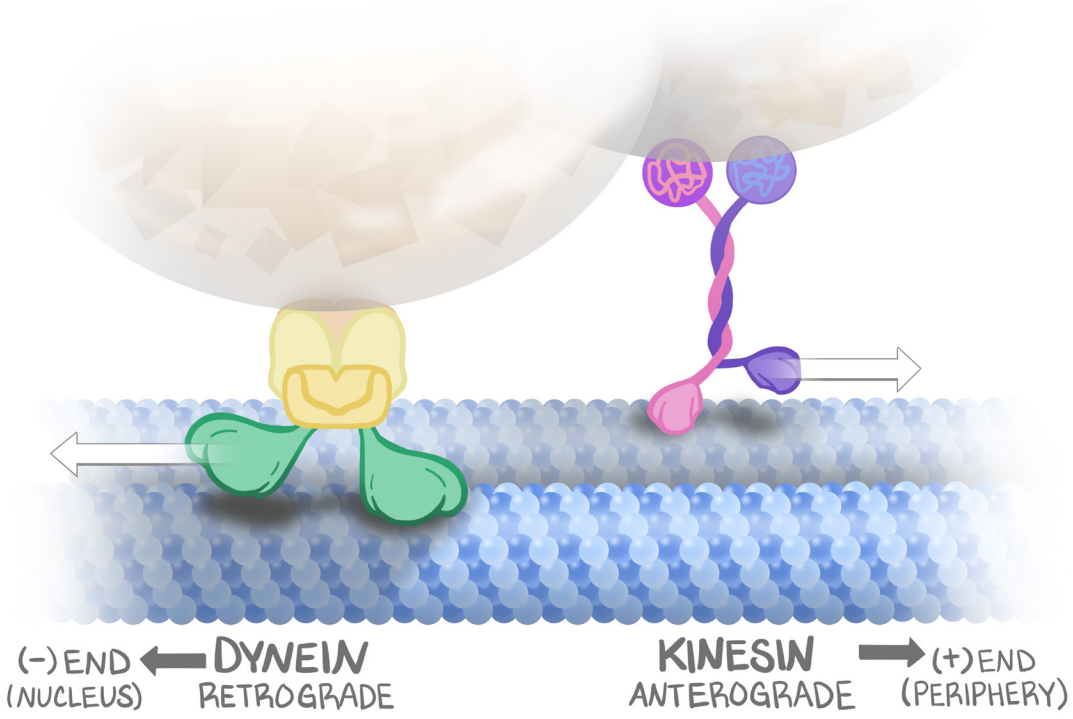
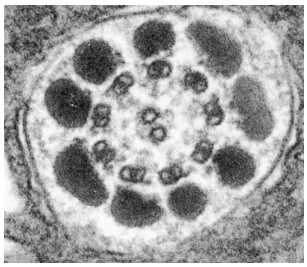


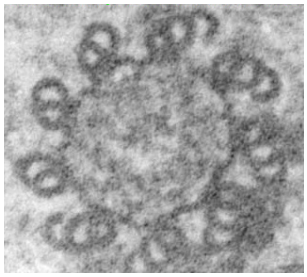
Figure 4.2: Motor Proteins and Vesicles
Microtubules act as tracks on which motor proteins carry vesicles. Dynein is a minus-end-directed (towards the nucleus) motor protein, whereas kinesin is a plus-end-directed (towards the cell membrane) motor protein.

Microtubules in Cilia and Flagella

Cilia and flagella have a more complex organization of microtubules, which requires a strong foundation, a **microtubule-organizing center (MTOC)**. You may have already learned about the centriole's function as the MTOC in mitosis, but we discuss that separately in the Inflammation and Neoplasia series. In the cilia and flagella, the **basal body** functions as the MTOC.



(a)



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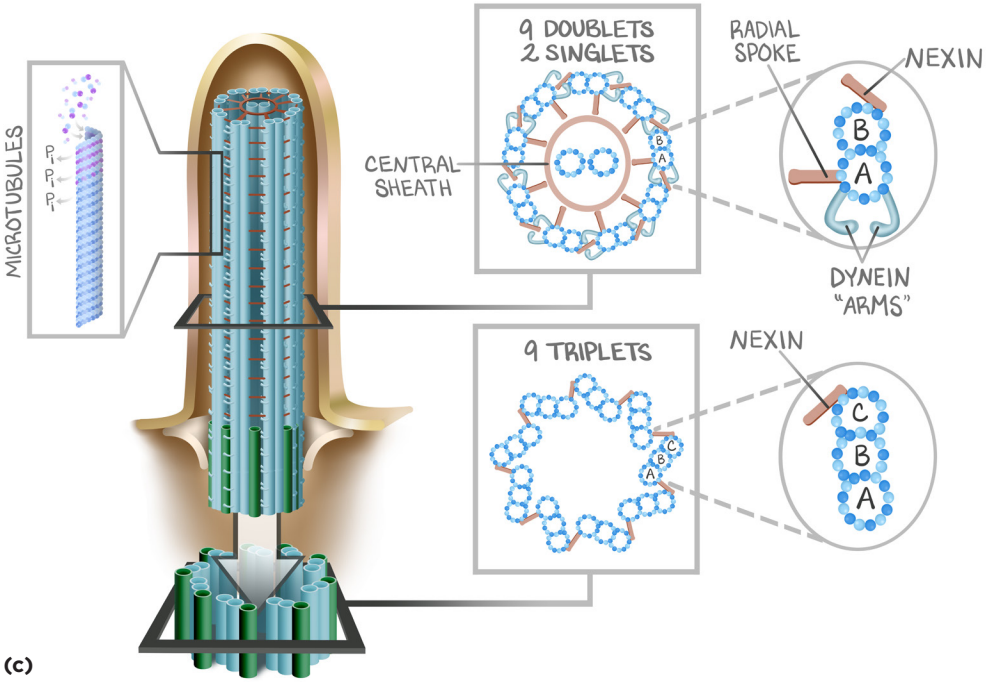

(c)

Figure 4.3: Cilia and Microtubules
(a) Electron micrograph (EM) showing the MTOC, the basal body, with 9 triplets and 0 inner doublets. (b) EM showing the axoneme, with 9 doublets and 2 singlets. (c) Artist's rendition of the cilia, demonstrating the basal body anchoring the axoneme, the axoneme, and the orientation of the doublets to the singlets.

The **basal body** is the anchor for the flagella/cilia, and is just below the plasma membrane. The basal body has **no central microtubules** and **nine triplet microtubules.** The cilia themselves will each have **two central singlet** microtubules in the middle of a ring of **nine doublet microtubules** (two microtubules next to each other) surrounding the singlets. **Nexin** glues the doublets together, so that they move as one unit. **Dynein** uses its head to pull the neighboring microtubule, which generates a coordinated synchronized movement, providing the force needed for mobility of the appendage (cilium) or the organism (flagellum).

Microfilaments

Actin makes up microfilaments. We see actin in skeletal muscle contraction, but it's also a key component in the peripheral cytoskeleton. Actin fibers exist just under the cytoplasm. They're the support structure for microvilli and maintain morphology of the cell. Microfilaments are also utilized in cytokinesis (the end of mitosis) and in podocyte mobility (renal glomerulus). We'll discuss later how they interact with the ECM and other cells (#9: *Epithelium*), along with their roles in skeletal muscle (#14: *Skeletal Muscle*). The juicier details of actin polymerization, the stuff you'd expect to find in histology or physiology textbooks, is really just not worth the squeeze.

Intermediate Filaments

Intermediate filaments are actually the "skeleton" of the **cytoskeleton**. They are attached to desmosomes and provide lateral tensile strength between two cells. They maintain the cell structure and thus are very limited in the way of mobility. The reproducible pattern according to which certain cells express certain intermediate filaments allows us to use **immunohistochemistry staining** to identify cells under a microscope. Though clinically useful, memorizing all the families of proteins and their associated cells and cancers is of low yield. However, there are some of higher yield, including **keratins** (most tested), **vimentins**, **desmins**, and **glial fibrillary acid proteins (GFAP)**. We'll discuss later some additional utility of intermediate filaments (#9: *Epithelium*).

STAIN	CELL	CANCERS
Cytokeratin	Epithelial cells	Squamous cell carcinoma
Vimentin	Mesenchymal tissue (fibroblasts, macrophages)	Mesenchymal tumors (sarcoma)
Desmin	Muscle	Muscle tumors Rhabdomyosarcoma
GFAP	Glial cells	Glioblastoma multiforme
Neurofilaments	Neurons	Neuroblastoma

Table 4.1: Utility of Intermediate Fibers
Learning these now may not be high-yield, but the table shows how the nebulous "intermediate fibers" go beyond cell physiology and demonstrates their utility in pathologic diagnosis.

Citations

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